The influence of depression and neuroinflammation on the progression of mild cognitive impairment to dementia: PET imaging of amyloid deposition and microglia activation

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To investigate the effect of late onset depression and inflammation on the pathological progression from MCI to Alzheimer*s disease by determining the correlation of microglia cell activation, β-amyloid deposition, brain volume, peripheral...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Structural brain disorders
Study type	Observational invasive

Summary

ID

NL-OMON32861

Source
ToetsingOnline

Brief title
Neurobiology of mild cognitive impairment

Condition

- Structural brain disorders
- Dementia and amnestic conditions

Synonym
late onset depression, Mild cognitive impairment

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: In eigen beheer

Intervention

Keyword: Depression, Inflammation, Mild cognitive impairment

Outcome measures

Primary outcome

Quantification of alterations of brain beta-amyloid and activated microglia on

the progress of dementia in patients with mild cognitive impairment and late

onset depression determined with PET.

Secondary outcome

• Plasma pro-inflammatory proteins as well as brain derived neurotrophic factor.

• Cognition.

• Alterations in brain volume

Study description

Background summary

Mild cognitive impairment (MCI) can be defined as a transitional phase between normal ageing and dementia disorders and is associated with a highly increased risk for dementia due to Alzheimer*s disease. MCI is a stage in which early neuropathology of dementia, especially Alzheimer*s disease occurs, but do not meet the clinical criteria. Recent studies have also shown that presence of late onset depression in patients significantly contributes to the progression of dementia. The ability to detect subjects with MCI has attracted a lot of interest due to the possibility that this might be the earliest stage at which treatments for dementia, particularly Alzheimer*s disease can be attempted to prevent irreparable damage that occurs with the progression of this disease. The main pathological features in the Alzheimer*s brain are progressive depositions of proteins called β-amyloid between nerve cells and neurofibrillary tangles within the nerve cells that accumulate abnormally in a

predictable spatial pattern throughout the brain. β-amyloid begin to accumulate in the brain in persons with MCI, where the plaques become more prevalent and spread with the progression to Alzheimer*s disease. Microglia cells acts as immune cells in the brain and are the first elements to respond after any kind of disturbance in the brain. Under certain pathological conditions, such as Alzheimer*s disease, resting microglia undergo microglia activation. This is characterized by the proliferation and migration of microglia to the affected area and increased production of pro-inflammatory mediators, including deleterious free radicals and pro-inflammatory cytokines that are capable of initiating or exacerbating the progression of Alzheimer*s disease pathology. Cytokines are signalling proteins that play a pivotal part in the regulation of the immune system. Human studies have provided considerable evidence in favour of the view that abnormalities of cytokines contribute to the evolution of psychiatric disturbances, including depression and dementia. Studies have also shown that increased levels of cytokines in the brain plays a pivotal role in neurodegenerative disorders. Depression, inflammation and inflammatory causing factors may not only independently influence the progression of MCI to Alzheimer*s disease, but may also work synergistically or additively with each other in the progression of neurodegeneration. However, no research to our knowledge has been done in order to determine the combined influences of depression, neuroinflammation and β-amyloid, which are three of the major factors in the pathogenesis to neurodegeneration.

Study objective

To investigate the effect of late onset depression and inflammation on the pathological progression from MCI to Alzheimer*s disease by determining the correlation of microglia cell activation, β-amyloid deposition, brain volume, peripheral inflammatory markers (IL-1β, TNF-α, INF- α and IL-6), peripheral brain derived neurotrophic factor and cognition of healthy volunteers compared to patients with late onset depression in the presence or absence of MCI.

Study design

This will be a follow up study to determine the correlation of MCI, depression and inflammation in the progression of neurodegeneration of Alzheimer*s disease. After informed consent of the volunteers had been obtained healthy volunteers, patients with late onset depression, patients with MCI and patients with MCI and late onset depression will undergo an examination and a battery of tests to determine whether they have met the requirements for one of the abovementioned groups. The examination will include psychiatric tests that will be done to evaluate the presence and degree of depression. Neuropsychological assessment will be done to aid in the diagnosis of MCI. After a diagnosis of one of the abovementioned criteria, a structural brain imaging using high resolution magnetic resonance imaging (MRI) will be done on all of the abovementioned participants to determine the presence of vascular

lesions and structural brain volume. Volunteers will be excluded of the study if the presences of cerebral vascular lesions or cerebral cancer have been identified with MRI. The PET procedures will continue on healthy volunteers, patients with late onset depression and patients with MCI but not on patients who has MCI together with late onset depression after a volunteer has met the requirements for one of the abovementioned groups. The same procedures will be repeated 18 months later.

Study burden and risks

Not applicable

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Informed consent
• Aged between 50-80 years
• Assigned by physician as competent to participate in the study
• Inclusion groups:
o Fulfilling the criteria for healthy volunteers
o Fulfilling the criteria for late onset depression
o Fulfilling the criteria for MCI
o Fulfilling the criteria for both late onset depression and MCI

Exclusion criteria

• History of major psychiatric disorders such as schizophrenia and bipolar disorder and previous unipolar depression
• History of head trauma
• Ischemic cerebrovascular disease, determined by MRI
• Major medical illnesses such as coronary heart disease, diabetes and cancer
• Chronic inflammatory disease such as rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, psoriasis, etc.
• Use of anti-inflammatory medication such as non-steroidal anti-inflammatory drugs (NSAID) and corticosteroids during a week before PET scan
• The use benzodiazepines a week before the PET scan
• The use of statins, acetylcholinesterase inhibitors, warfarin and digoxin
• History of substance abuse such as alcohol and nicotine (smoking) within the last 6 months
• Presence of dementia
• Any patients with MRI contradictions such as metal implantations and pacemakers
• Malnutrition (vitamin deficiency) or obesity (BMI > 30)

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-07-2019
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	11C-PIB and 11C-PK11195

Ethics review

Approved WMO

Date:	23-12-2008
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-008445-37-NL
CCMO	NL24114.042.08